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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JOYCE, CATHERINE	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/738,404	THORPE ET AL.
	Examiner	Art Unit
	Catherine M. Joyce	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *18 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-12,25,29-31,34-39,41,42 and 46-51* is/are pending in the application.

4a) Of the above claim(s) *36-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-12,25,29-31,34,35,41,42 and 46-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The Amendment filed September 18, 2006 in response to the Office Action of March 15, 2006 is acknowledged and has been entered. Previously pending claims 3-12, 25, 29-31, 34, 35, 41, 42, 46 and 47, and new claims 48-51 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are being maintained:

Claim Rejections - 35 USC 112

4. The establishment of a priority date of April 28, 1998 for claims 3-12, 25, 29-31, 34, 35, 41, 42, 46 and 47 is maintained, and is newly established for claims 48-51, for the reasons set forth previously in the Paper mailed March 15, 2006, Section 5, pages 3-4.

Applicant argues that the present application is entitled to a priority date of April 28, 1999, the filing date of application Serial No. 60/131,432. Applicant argues that the '432 specification teaches at page 118 that the 2C3-based antibody treatment methods of the invention may be combined with tumor and disease treatment methods, including combinations with other anti-cancer agents. Applicant further argues that the '432 specification, on page 119, refers to well known uses of combinations of substances in cancer treatment, wherein the first combination mentioned are prodrugs as exemplified by U.S. Patent No. 5,710,134, which was incorporated by reference.

Applicant's arguments have been considered but have not been found to be persuasive for the following reasons. The teaching of the '432 specification at page 118 that 2C3-antibody based treatment methods of the invention may be combined with other tumor and disease treatment methods does not provide support for the specific combination of "(i) a first immunoconjugate that comprises a cleavage agent or enzyme operatively attached to an anti-VEGF antibody, or antigen-binding fragment thereof that binds to substantially the same epitope as the monoclonal antibody 2C3 and (ii) subsequently administering to the animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by the

cleavage agent or enzyme attached to the antibody" as is instantly claimed. Further, the teaching of the '432 specification on page 119 with regard to prodrugs teaches specifically the following:

> The general used of combinations of substances in cancer treatment is well know (sp). For example, U.S. Patent No. 5,710,134 (incorporated herein by reference) discloses components that induce necrosis in tumors in combination with non-toxic substances or "prodrugs". The enzymes set free by necrotic processes cleave the non-toxic "pro-drug" into the toxic "drug", which leads to tumor cell death.

Thus, the prodrug/antibody combinations described in the specification are antibodies administered in conjunction with prodrugs that are cleaved by enzymes set free by necrotic processes and not the combination of "(i) a first immunoconjugate that comprises a cleavage agent or enzyme operatively attached to an anti-VEGF antibody, or antigen-binding fragment thereof that binds to substantially the same epitope as the monoclonal antibody 2C3 and (ii) subsequently administering to the animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by the cleavage agent or enzyme attached to the antibody" as is instantly claimed. Further, a review of the cited 5,710,134 patent, entitled "Combination of Necrosis-Inducing Substances With Substances With Substances Which Are Activated By Necroses For The Selective Therapy of Tumors And Inflammatory Disorders" shows this patent also describes antibodies administered in conjunction with prodrugs that are cleaved by enzymes set free by necrotic processes and not the instantly claimed combination. Thus, as set forth in the previous Office Action, claims 3-12, 25, 29-31, 34-39, 41, 42, 46 are assigned the priority date of April 28, 2000, the filing date of parent application no. 09/561,005 and claims 47-51 are assigned this same priority date for the same reasons. It is noted that while the previous Office Action inadvertently referred to application serial no. 09/508,251, this error appears to be harmless in that the proper filing date was assigned and the bases for this assignment were set forth.

5. Claim 9 remains rejected under 35 USC 112, second paragraph, for the reasons set forth previously in the Paper mailed March 15, 2006, Section 7, page 5.

With regard to the use of the term chimeric, Applicant argues that no support for the position that the exact meaning of the term "chimeric" was provided, that Applicant's recent search identified over 600 issued U.S. patents having claims that contain the term chimeric antibody, wherein such routine usage indicates contradicts the position that the term is indefinite, and that the objected to term occurs in the same context in the claims issued in the parent application, U.S. Patent No. 6,703,020.

Applicant's arguments have been considered but have not been found to be persuasive. The citation of the term in a large number of patents only indicates that the term is commonly employed and not that one of skill in the art would necessarily know the meaning thus the metes and bounds of the invention. Further, it is noted that each patent application is considered on its own merits and the use of the same term in related patent application is not determinative of the issue.

New Grounds of Rejection

Objections to the Claims

6. Claims 49 and 50 are objected to because of the following informalities: they are essentially duplicates of claims 48 and 47, respectively. Appropriate correction is required.

Claim Rejections - 35 USC 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 10, 48 and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating cancer comprising administering to animal a substantially inactive prodrug and a first immunoconjugate that comprises at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that binds to substantially the same epitope as the monoclonal antibody

2C3, wherein the immunoconjugates comprises variable regions that include the amino acid sequences of SEQ ID NO:7 and SEQ ID NO:9, does not reasonably provide enablement for a method for treating cancer comprising administering to animal a substantially inactive prodrug and a first immunoconjugate that comprises at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that binds to substantially the same epitope as the monoclonal antibody 2C3, wherein the immunoconjugates comprises variable regions that include the amino acid sequences of SEQ ID NO:7 or SEQ ID NO:9. This means, the claims as broadly drawn, encompass methods of using antibodies that comprise only the light chain or only the heavy chain of the monoclonal antibody 2C3.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to the following:

a method for treating cancer, comprising administering to an animal that has a vascularized solid tumor, a metastatic tumor or metastases from a primary tumor, a therapeutically effective amount of:

(a) a first pharmaceutical composition comprising at least a first immunoconjugate that comprises at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that binds substantially the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595), thereby localizing the immunoconjugate to the vasculature or stroma of said vascularized solid tumor, and

(b) subsequently administering to said animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by the cleavage agent or enzyme attached to said antibody in said first pharmaceutical composition, thereby releasing a substantially active drug specifically within the vasculature or stroma of said vascularized solid tumor,

wherein said at least first antibody of said immunoconjugate comprises at least a first variable region that includes an amino acid sequence region having the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:9 (claim 10);

a method for treating cancer, comprising administering to an animal that has a vascularized solid tumor, a metastatic tumor or metastases from a primary tumor, a therapeutically effective amount of:

(a) a first pharmaceutical composition comprising at least a first immunoconjugate that comprises at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that binds substantially the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595), thereby localizing the immunoconjugate to the vasculature or stroma of said vascularized solid tumor, and

(b) subsequently administering to said animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by the cleavage agent or enzyme attached to said antibody in said first pharmaceutical composition, thereby releasing a substantially active drug specifically within the vasculature or stroma of said vascularized solid tumor,

wherein said at least first antibody, or antigen binding fragment thereof, of said immunoconjugate comprises at least a first variable region that includes an amino acid sequence region having the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:9 (claim 48 and 49);

The specification teaches an anti-VEGF antibody (2C3) that specifically inhibits VEGF binding to the VEGR2 receptor, that has significant anti-tumor effects in-vivo, and that does not inhibit VEGF binding to the VEGFR1 receptor. The specification further teaches that the sequences of SEQ ID NO:7 and SEQ ID NO:9 are the sequences of Vh (variable region of the heavy chain) and Vκ (variable region of the light chain), encompassing CDR1-3 (complementarity determining regions) of the variable regions of the heavy and light chains (page 21, lines 22-29) of the 2C3 antibody (page 21, lines 22-29).

The teaching of the specification cannot be reasonably extrapolated to the scope of the claims because one of skill in the art could not predict that a functional antibody the comprises the Vh region of the 2C3 antibody without the Vκ region, or the Vκ of the 2C3 antibody without the Vh region, (i.e. an antibody that comprises SEQ ID NO:7 or SEQ ID NO:9) could be made or that it would bind to substantially the same epitope as the monoclonal antibody 2C3. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs, in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Thus, it is unlikely that antibodies which comprise less than the full complement of CDRs from the heavy and light chain variable regions of the 2C3 antibody can be made or will function as claimed. The specification provides no direction or guidance regarding how to produce

antibodies having the recited binding capabililty wherein the antibodies comprise Vh region of the 2C3 antibody without the Vκ region, or the Vκ of the 2C3 antibody without the Vh region. Therefore, in view of the lack of guidance in the specification on making functional antibodies that comprise the Vh region of the 2C3 antibody without the Vκ region, or the Vκ of the 2C3 antibody without the Vh region, and the teaching in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, it cannot be predicted that functional antibodies having the recited structure can be made. Therefore, undue experimentation would be required to practice the claimed invention.

Some of Applicant's arguments drawn to the rejection of claim 10 in the previous Office Action are relevant to the instant rejection. Applicant argues that the claim language is drawn to an antibody that *comprises* a first variable region that includes an amino acid sequence region having the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:9 and the transitional phrase means that the named elements are essential, but other elements may be added, and thus the previous Action's reading of claim 10 as meaning only the Vh or Vκ regions, but not both is inconsistent with standard claim interpretation rules because claim 10 clearly covers antibodies comprising both Vh and Vκ regions.

Applicant further argues that, even as to an antibody containing only a Vh or Vκ region, without the other, the rejection is improper as it does not provide sufficient reason doubt the specification and ignores the well established field of single domain antibodies. In particular Applicant cites Ward et al. (1989, Nature 341(6242):544-6) as Exhibit E, numerous publications form the early 1990's onwards as Exhibit F, pages from the Domantis website as Exhibit G, and pages from the Ablynx website as Exhibit H, references related to camelid antibodies (Riechman Muyldermans, 1999, J. Immunol. Methods 231:25-38; Muyldermans et al., 2001, TIBS 26(4):230-235) as exhibit I. It is noted that the Response to Office Action was not found to contain any of the above cited references and thus these references could not be particularly considered. Applicant further argues that the existence of the naturally occurring single domain camelid antibodies contradicts the proposition set forth in the previously issued

Office Action that single domain antigen binding sites cannot be made or function because such antibodies have existed naturally for millennia. Applicant further argues that the use of camelised type single domain antibodies in real-world biotechnology also pre-dates the present application's priority date and was, at that time, already covered by the existence of issued U.S. patents U.S Patent Nos. 5,759,808, 5,800,988, and 5,840,526. Applicant further cites the ongoing issuance of U.S. Patents in this field such as U.S. Patent Nos. 6,005,079; 6,015,695; and 6765087, and the Domantis patents of Exhibit G. Again it is noted that the Domantis patents of Exhibit G were not found in the response to the Office Action and thus these references could not be specifically considered.

Applicant's arguments have been considered but have not been found to be persuasive. Contrary to Applicants arguments, the state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions which provide the majority of the contact residues for the binding of the antibody to its target epitope. While applicant cites references that teach single domain antibodies, these are exceptions to the standard prototypic immunoglobulin molecule comprising all six CDRs in the context of framework sequences which maintain their required conformation to produce an antibody having antigen-binding function. Thus, Applicant's arguments drawn to camelid antibodies are essentially arguing limitations not found in the claims as the claims are not drawn to or limited to camelid antibodies and one of skill in the art would not expect that antibodies that are not camelid antibodies would function as claimed because of the known differences in structure between prototypical antibodies and camelid antibodies. Further, the specification did not provide any working examples that antibodies other than antibodies the contained the full complement of CDRs would function as claimed. Thus, as set forth above and in the previous Office Action, practice of the invention would require undue experimentation.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 3-6, 8, 9-12, 25, 41, 42 and 4-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brekken et al. (1998, Cancer Research 58:1952-1959) in view of Melton et al.

(1996, J. of the National Cancer Institute 88(3/4):153-165) and Presta et al. (1997, Cancer Res. 57(20):4593-9) (abstract).

The claims are drawn to the following: a method for treating cancer, comprising administering to an animal that has a vascularized solid tumor, a metastatic tumor or metastases from a primary tumor, a therapeutically effective amount of (a) a first pharmaceutical composition comprising at least a first immunoconjugate that comprises at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that binds substantially the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595), thereby localizing the immunoconjugate to the vasculature or stroma of said vascularized solid tumor, and (b) subsequently administering to said animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by the cleavage agent or enzyme attached to said antibody in said first pharmaceutical composition, thereby releasing a substantially active drug specifically within the vasculature or stroma of said vascularized solid tumor (claim 5),

wherein said immunoconjugate binds to VEGF bound to the VEGF receptor VEGFR1 expressed by endothelial cells of the vasculature of said vascularized tumor (claim 3),

wherein said immunoconjugate binds VEGF bound within the stroma of said vascularized tumor (claim 4),

wherein at least a first antibody of said immunoconjugate is a monoclonal antibody or an antigen-binding fragment thereof (claim 6),

wherein said at least first antibody of said immunoconjugate is a human, humanized or part-human antibody or antigen-binding fragment thereof (claim 8),

wherein said at least first antibody of said immunoconjugate is a chimeric antibody or a recombinant antibody (claim 9),

wherein said at least first antibody of said immunoconjugate is the monoclonal antibody 2C3(ATCC PTA 1595) (claim 11),

wherein said at least first antibody is operatively attached to two or more cleavage agents or enzymes (claim 12)

wherein said immunoconjugate comprises the at least a first antibody operatively attached to the at least a first cleavage agent or enzyme as fusion protein prepared by expressing a recombinant vector that comprises, in the same reading frame, a DNA segment encoding the antibody operatively linked to a DNA segment encoding the cleavage agent or enzyme (claim 25),

wherein said at least a first cleavage agent or enzyme and said at least one substantially inactive prodrug are operably matched agents selected from the groups consisting of: (a) alkaline phosphatase, arylsulfatase, serratia protease, thermolysin, subtilisin, a carboxypeptidase, a cathepsin, D-alanylcarboxypeptidase, .beta.-galactosidase, neuramimidase, .beta.-lactamase, penicillin amidase and cytosine deaminase; and (b) a phosphate-containing prodrug, sulfate-containing prodrug, peptide-based prodrug, D-amino acid-modified prodrug, glycosylated prodrug, .beta.-lactam-containing prodrug, optionally substituted phenoxyacetamide- or phenylacetamide-containing prodrug and 5-fluorocytosine (claim 41),

wherein said animal is a human patient (claim 42),

wherein said immunoconjugate localizes to the vasculature and stroma of said vascularized tumor (claim 47 and 50),

wherein said at least first antibody, or antigen binding fragment thereof, of said immunoconjugate comprises at least a first variable region that includes an amino acid sequence region having the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:9 (claim 48 and 49)

and

a method for treating cancer, comprising administering to an animal that has a vascularized solid tumor:

(a) a first composition comprising at least a first immunoconjugate that comprises at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that effectively competes with the monoclonal antibody 2C3 (ATCC PTA 1595) for binding to VEGF, thereby localizing said immunoconjugate to the vasculature or stroma of said vascularized solid tumor; and

(b) subsequently administering to said animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by the cleavage agent or enzyme attached to said antibody in said first composition, thereby releasing a substantially active drug specifically within the vasculature or stroma of said vascularized solid tumor (claim 46)

a method for treating cancer, comprising administering to an animal that has a vascularized solid tumor, a metastatic tumor or metastases from a primary tumor, a therapeutically effective amount of

(a) a first pharmaceutical composition comprising at least a first immunoconjugate that comprises at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that binds substantially the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595), thereby localizing the immunoconjugate to the tumor vasculature, and

(b) subsequently administering to said animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by the cleavage agent or enzyme attached to said antibody in said first pharmaceutical composition, thereby releasing a substantially active drug specifically within the vasculature of said vascularized solid tumor (claim 51).

Brekken et al. teaches anti-VEGF antibody (2C3) that blocks the interaction between VEGF and the VEGF receptor KDR/Flk-1, that inhibits VEGF-mediated growth of endothelial cells in vitro, and that localizes strongly to connective tissue in tumors after injection into mice bearing human tumor xenografts (abstract). Brekken also teaches that biotinylated 2C3 produced intense staining of connective tissue surrounding the vasculature of the H358 human NSCLC tumor after i.v. injection, with large tracks of stromal tissue that connect the tumor cell nests being stained with 2C3 and the most intense localization being observed in the largest tracks of stroma (page 1956). Brekken also teaches that endothelial cells in vessels not surrounded by stroma, such as vessels running through nest of tumor cells themselves were stained in some cases (page 1956). Brekken also teaches that 2C3 is potentially a vehicle for targeting therapeutic agents to tumor connective tissue (1958).

Brekken teaches as set for above but does not specifically teach a method of treating cancer comprising administering an anti-VEGF antibody having a cleavage agent or enzyme operatively attached and administering an inactive prodrug that is cleaved by the cleavage agent or enzyme thereby releasing a substantially active drug specifically within the vasculature or stroma of the tumor.

Presta et al. teaches that a murine anti-human VEGF monoclonal antibody A.4.6.1 has been shown to potently suppress angiogenesis and growth in a variety of human tumor cell lines transplanted into nude mice and that a humanized version of the antibody inhibits VEGF-induced proliferation of endothelial cells in vitro and tumor growth in vivo with potency and efficacy very similar to those of the murine antibody (abstract). Presta suggests that inhibition of VEGF-induced angiogenesis with an anti-VEGF antibody is a valid strategy for the treatment of solid tumors in humans (abstract).

Melton teaches that the use of antibody-enzyme conjugates directed at tumor-associated antigens to achieve site-specific activation of prodrugs to potent cytotoxic species, termed "antibody-directed enzyme prodrug therapy" (ADEPT), has a particular advantage in that it may allow the use of potent agents that are too toxic to be used in conventional chemotherapy (abstract). Melton also teaches that the ADEPT system offers the potential to overcome problems associated with drug or toxin immunoconjugates including that such as lack of expression of a target antigen on all tumor cells and the fact that antibodies penetrate tumors poorly (page 153, second column thru page 154, first column). Melton also teaches fusion proteins comprising both antigen-binding and enzymatic activities and humanized antibodies (abstract). Melton also teaches that the enzyme/prodrug systems may comprise carboxypeptidase G2, carboxypeptidase G2, carboxypeptidase A, alkaline phosphatase, penicillin amidase, β-glucuronidase, β-lactamase, and cytosine deaminase and associated substrates (Table 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the anti-VEGF tumor targeting 2C3 antibody of Brekken in the VEGF-targeted antibody immunotherpay methods for the treatment of tumors as described by

Presta and to employ the antibody-directed enzyme prodrug therapy of Melton in conjunction with the 2C3 antibody. One of ordinary skill in the art would have been motivated to substitute the antibody of Brekken, as modified according to Melton, for the antibody described by Presta because of the teaching in Brekken that the 2C3 antibody localizes strongly to tumors and thus both an anti-VEGF and tumor targeting effect could be obtained, especially in view of Brekkens express suggestion that the anti-VEGF antibody 2C3 be used for tumor targeting. One of skill in the art would have had a reasonable expectation of success in making the substitution of the 2C3 antibody in the treatment method of Presta and in using the ADEPT system in conjunction with the 2C3 antibody because of the stated success in Presta of anti-VEGF antibodies in inhibiting tumor growth, the teaching in Brekken that the anti-VEGF 2C3 antibody localizes strongly to tumors, and the stated success in Melton of using the ADEPT system with tumor immunotherapy. One of skill in the art would have been motivated to attach two or more cleavage agents or enzymes to the antibody, and would have had a reasonable expectation of success in doing so, because of the advantages that could be expected from multiple cleavage agent or enzyme attachments in terms of efficiency of enzyme or cleavage agent conversion of the prodrug. That is, a higher concentration of cleavage agents or enzymes at the tumor target site would be expected to generate a greater local concentration of active drug and therefore result in enhanced anti-tumor activity.

It is note that while the exact sequences of the SEQ ID Nos:7 and 9 are not disclosed by Brekken, they are the sequences of the heavy and light chains of the 2C3 antibody and thus they are inherently disclosed by the teaching in Brekken.

Some of Applicant's arguments drawn to the rejection of claim 3-6, 8, 9, 11, 12, 25, 41, 42 and 46 under 35 USC 103 in the previous Office Action are relevant to the instant rejection. Applicant argues that the claimed invention is entitled to a priority date of April 28, 1999 and thus that Brekken (published May 1, 1998) is available as prior art under 35 USC § 102(a) and can be removed as prior art by identifying the non-inventive contribution of the listed co-authors (i.e. a Katz declaration).. Applicant thus submits for consideration a Katz declaration that was filed in the parent application. Applicant further argues that even if Brekken is available as prior

art the 103 rejection is overcome because Melton teaches away from the claimed invention because Melton teaches that the antigen targeted by an ADEPT antibody should not circulate at high levels since this will act as a competitor for antibody binding and abnormally high levels of VEGF were known to be associated with various cancers as exemplified by Jinno et al. (1998, J. Gastroenterol. 33(3):376-82). Applicant further argues that the antibody of Presta cannot be used as targeting agent as it binds only to free VEGF and not to VEGF docked in any receptor and that by providing such an antibody that cannot be used in ADEPT, Presta teaches away from the proposed combination with Melton. Applicant further argues that the rejection is not rescued by Brekken because the only binding property of the 2C3 antibody described in Brekken is that it blocks VEGF binding to the VEGF receptor KDR/Flk-1.

Applicant's arguments have been considered but have not been found to be persuasive. With regard to Applicant's arguments that the claimed invention is entitled to priority date of April 28, 1999 and that Brekken (published May 1, 1998) is thus not available as prior art under 35 U.S.C 102(b), it is noted that, as discussed in paragraph 4 above, the priority date for the rejected claims is maintained as April 28, 2000.

With regard to Applicant's argument that Melton teaches away from the claimed invention because Melton teaches at page 154 that the antigen targeted by an ADEPT antibody should not circulate at high levels since this will act as a competitor for antibody binding, this argument is not found to be persuasive because the cited teaching is not found in Melton. Melton actually states that "[a]lthough shed antigen present in the circulation will act as a competitor with the tumor site for binding of target antigen, there is evidence that tumor localization of conjugate can occur in the face of circulating antigen unless levels of the later are particularly high." It is noted that the cited Jinno reference could not be particularly considered because the cited reference was not provided as part of the response to the Office Action. With regard to Applicant's argument that the antibody of Presta cannot be used as targeting agent as it binds only to free VEGF and not to VEGF docked in any receptor and that Presta thus teaches away from the proposed combination with Melton, this argument is not found be persuasive because the cited teaching of Presta that the antibody binds only to free VEGF is not found in

Presta. Further, Applicant's argument that the rejection is not rescued by Brekken because the only binding property of the 2C3 antibody described in Brekken is that it blocks VEGF binding to the VEGF receptor KDR/Flk-1 is not found to be persuasive because as set forth in the previous Office Action, Brekken teaches the following: that biotinylated 2C3 produced intense staining of connective tissue surrounding the vasculature of the H358 human NSCLC tumor after i.v. injection, with large tracks of stromal tissue that connect the tumor cell nests being stained with 2C3 and the most intense localization being observed in the largest tracks of stroma (page 1956); that endothelial cells in vessels not surrounded by stroma, such as vessels running through nest of tumor cells themselves were stained in some cases (page 1956); that 2C3 is potentially a vehicle for targeting therapeutic agents to tumor connective tissue (1958).

11. Claims 5, 7, 29-31, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brekken et al. (1998, Cancer Research 58:1952-1959) in view of Presta et al. (1997, Cancer Res. 57(20):4593-9) (abstract) and Melton et al. (1996, J. of the National Cancer Institute 88(3/4):153-165), and further in view of US Patent No. 5,863,538 and US Patent No. 5,621,002.

The claims are drawn to the following: a method for treating cancer, comprising administering to an animal that has a vascularized solid tumor, a metastatic tumor or metastases from a primary tumor, a therapeutically effective amount of (a) a first pharmaceutical composition comprising at least a first immunoconjugate that comprises at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that binds substantially the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595), thereby localizing the immunoconjugate to the vasculature or stroma of said vascularized solid tumor, and (b) subsequently administering to said animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by the cleavage agent or enzyme attached to said antibody in said first pharmaceutical composition, thereby releasing a substantially active drug specifically within the vasculature or stroma of said vascularized solid tumor (claim 5),

wherein said at least first antibody of said immunoconjugate is an scFV, Fv, Fab', Fab, diabody, linear antibody or $F(ab')_2$ antigen-binding fragment of an antibody (claim 7),

wherein said a first pharmaceutical composition is administered to said animal intravenously (claim 29),

further comprising subjecting the animal to radiotherapy (claim 30),

further comprising administering to the animal a therapeutically effective amount of at least a second anti-cancer agent (claim 31),

wherein said at east a second anti-cancer agent is a chemotherapeutic agent (claim 34).

wherein said at least a second anti-cancer agent is colchicine, taxol, vinblastine, vincristine, or vindescine, or tumor-targeted form thereof (claim 35),

Brekken, Presta, and Melton teach as set forth above but do not specifically teach the intravenous administration of the immunoconjugate, the use of antibody that is an scFV, Fv, Fab', Fab, diabody, linear antibody or $F(ab')_2$ antigen binding fragment of an antibody, or the further administration of radiotherapy or a second cancer agent that is a chemotherapeutic agent, or the administration of colchicines, taxol, vincristine, or vindescine as the second therapeutic agent.

US Patent No. 5,863,538 teaches that, for vascular targeted tumor therapies, including immunotherapy, target cells are directly accessible to intravenously administered therapeutic agents, permitting rapid localization to a high percentage of the injected dose (column 3, lines 17-20). US Patent No. 5,863,538 teaches that advantages will be realized through combination regimens wherein both the tumor vasculature and the tumor itself are targeted, and that combination regimens may thus include targeting of the tumor directly with either conventional antitumor therapy, such as with radiotherapy or chemotherapy (column 14, line 56 thru column 15, line 9). US Patent No. 5,863,538 teaches that anticancer agents that may be employed include a steroid, an antimetabolite, an anthracycline, a vinca alkaloid, an antibiotic, an alkylating agent or an epipodophyllotoxin, or a plant-, fungus- or bacteria-derived toxin (claims 15 and 16). Exemplary antineoplastic agents that have been investigated include doxorubicin, daunomycin, methotrexate, vinblastine (column 43, lines 65-67). US Patent 5,863,538 further teaches that antibodies may be univalent fragments such as Fab' or Fab (column 5, lines 2-7).

US Patent No. 5,621,002 teaches that pharmacologically active substances for use in anti-tumor therapy, particularly for use as prodrugs, include vindesine, vincristine, vinblastine, colchicine, and taxol

It would have been obvious to combine the teaching of Presta, Brekken and Melton on the use of the tumor vasculature targeted 2C3 antibody conjugated to an enzyme or cleavage agent in conjunction with a prodrug for tumor therapy with the teaching of US Patent No. 5,863,538 on the intravenous administration of immunoconjugates, on the use of tumor vasculature targeted antibody therapies in conjunction with other anti-cancer therapies such as radiotherapy or chemotherapy, and on use of antibody fragments because of the advantages

taught by US Patent No. 5,863,538 on intravenous administration and on using tumor vasculature targeted immunotherapies in conjunction with other anti-tumor therapies and because of the teaching in US Patent No. 5,863,538 of the art recognized equivalence of antibody and antibody fragments. One would have had a reasonable expectation of success because of the success demonstrated in US Patent No. 5,863,538.

Further, it would have obvious to combine the teaching of Brekken, Melton, and US Patent No. 5,863,538 on the use of antibody conjugate/prodrug therapy in combination with a second therapeutic agent with the teaching of US Patent No. 5,621,002 on vindesine, vincristine, vinblastine, colchicine, and taxol as chemotherapeutic agents. One would have had a reasonable expectation of success because of the known pharmacological activity of vindesine, vincristine, vinblastine, colchicine, and taxol as described in US Patent No. 5,621,002.

12. No claims allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8700.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Susan Ungar

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Catherine M. Joyce
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